Title
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Journal
Environmental health perspectives, 110(9)

ISSN
0091-6765

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Publication Date
2002-09-01

DOI
10.1289/ehp.02110955

Peer reviewed

Critical Windows of Exposure to Household Pesticides and Risk of Childhood Leukemia

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The potential etiologic role of household pesticide exposures was examined in the Northern California Childhood Leukemia Study. A total of 162 patients (0–14 years old) with newly diagnosed leukemia were rapidly ascertained during 1995–1999, and 162 matched control subjects were randomly selected from the birth registry. The use of professional pest control services at any time from 1 year before birth to 3 years after was associated with a significantly increased risk of childhood leukemia [odds ratio (OR) = 2.8; 95% confidence interval (CI), 1.4–5.7], and the exposure during year 2 was associated with the highest risk (OR = 3.6; 95% CI, 1.6–8.3). The ORs for exposure to insecticides during the 3 months before pregnancy, pregnancy, and years 1, 2, and 3 were 1.8 (95% CI, 1.1–3.1), 2.1 (95% CI, 1.3–3.5), 1.7 (95% CI, 1.0–2.9), 1.6 (95% CI, 1.0–2.7), and 1.2 (95% CI, 0.7–2.1), respectively. Insecticide exposures early in life appear to be more significant than later exposures, and the highest risk was observed for exposure during pregnancy. Additionally, more frequent exposure to insecticides was associated with a higher risk. In contrast to insecticides, the association between herbicides and leukemia was weak and nonsignificant. Pesticides were also grouped based on where they were applied. Exposure to indoor pesticides was associated with an increased risk, whereas no significant association was observed for exposure to outdoor pesticides. The findings suggest that exposure to household pesticides is associated with an elevated risk of childhood leukemia and further indicate the importance of the timing and location of exposure. *Key words:* **case–control studies, child, herbicides, insecticides, leukemia, pesticides.** *Environ Health Perspect* **110:955–960 (2002). [Online 14 August 2002]**
http://ehpnet1.niehs.nih.gov/docs/2002/110p955-960ma/abstract.html

Most studies evaluating the relationship between household pesticide exposures and childhood leukemia suggest that an increased risk of leukemia is associated with *in utero* and postnatal pesticide exposures (*1,2*). Nevertheless, previous studies have a number of limitations. Some of the estimated odds ratios (ORs) are not precise; that is, they have wide confidence intervals (*3–5*). Some studies have relatively low response rates (*5–7*) or are based on small numbers of cases (*3,4,6,8,9*). In addition, several study design issues could have contributed to problems in recall and reporting of household pesticide exposures, including source and recruitment of controls, matching criteria, method and timing of data collection, imprecise time intervals for which exposure data were collected, definition of exposure, and use of surrogate respondents. Because of the uncertainties in existing data, there is a compelling need to evaluate further the relationship between pesticide exposures and childhood leukemia, and to do so in studies with improved exposure classification and reduced differential reporting.

Methods

Study population. During the first phase (1995–1999) of the Northern California Childhood Leukemia Study (NCCLS), patients (0–14 years old) with newly diagnosed leukemia were rapidly ascertained from major clinical centers, usually within 24 hr after diagnosis. Although case ascertainment was hospital based, we compared the cases with those ascertained by the statewide population-based registry (*10*) and found that the NCCLS protocol successfully identified 88% of all newly diagnosed childhood leukemia cases in the San Francisco–Oakland metropolitan statistical area. Controls were randomly selected from the statewide birth certificate files maintained by the California Department of Health Services (Sacramento, CA) and 1:1 matched to cases on date of birth, sex, mother's race (white, black, or other), Hispanicity (either parent is Hispanic), and mother's county of residence at the time of child's birth. These controls were then traced by using commercially available searching tools. For cases not born in California (< 10% of all cases), county of residence at diagnosis was used for the matching. For each case, the search continued until an eligible control subject consented to participate in the study.

To be eligible, each case or control had to reside in the study area, be under 15 years of age at the time of diagnosis (or corresponding date for the control), have at least one parent or guardian who speaks English or Spanish, and have no previous history of any malignancy. Approximately 83% of the eligible cases consented to participate. Among all the eligible controls approached, 69% consented to participate. The study protocol was approved by the Institutional Review Boards of all collaborating institutions, and written informed consents were obtained for all participating subjects. A total of 162 matched case–control pairs are included in this analysis. Of the 162 patients, 135 had a diagnosis of acute lymphoblastic leukemia (ALL).

Data collection. In the NCCLS, detailed information on household pesticide use, including the name of each product, intended purpose (e.g., cockroach control), frequency of use, and time window of use (3 months before pregnancy, pregnancy, and years 1, 2, and 3), was collected through in-home personal interviews with the primary care giver, usually the biologic mother, shortly after diagnosis (corresponding dates for controls). For cases, the mean interval between diagnosis and in-home interview was 4.8 months. Because potential birth certificate controls needed to be identified from the birth registry and traced, the interview of a case usually preceded the interview of the corresponding control, with a mean lag time of 9.5 months.

Different types of pesticides were grouped for analysis. Unless the use of professional services was explicitly stated, all products were assumed to be personally applied. As defined in this article, insecticide exposures include professional pest control services, insect repellents, and the use of various products to control ants, flies, cockroaches, spiders, termites, and plant/tree insects; herbicide exposures include professional lawn service and the use of weed control products; flea control products include indoor foggers, flea collars, flea soaps or shampoos, and sprays, dusts, or powders for fleas. The use of flea control products is directly related to the presence of cats

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We thank J. Feusner, K. Matthay, S. Month, V. Crouse, K. Leung, and V. Kiley for assistance with recruiting patients and M. Does for supervising fieldwork.

The study was supported by grants from the National Institute of Environmental Health Sciences (PS42 ES04705 and RO1 ES09137). X.M. was supported by a grant from the Centers for Disease Control and Prevention (T01/CCT917644-01).

Received 14 November 2001; accepted 12 March 2002.

and/or dogs in the households, and the percentage of households in which the child had regular contact with cats and/or dogs during years 1 and 2 was different in cases (57%) and controls (65%). Therefore, flea control products were grouped as a separate category.

Individual products were also combined based on whether they were probably applied indoors or outdoors, although the questionnaire did not include specific questions about the exact location of pesticide application. As defined, indoor pesticide exposures include professional pest control service; products used to control ants, flies, cockroaches, spiders, or termites; insect repellent; and indoor foggers for fleas. Outdoor pesticide exposures include rat, mouse, gopher, or mole control products, slug or snail bait, and plant/tree insect control products.

Frequency indexes for insecticides and indoor pesticides, which were commonly administered in households, were calculated based on how often the products were used during a defined time window. For each product, scores of 0, 1, and 2 were assigned to "did not use," "used less than 5 times," and "used 5 or more times," respectively. Occasionally, when a respondent could not recall the exact frequency of use (~0.6% of all products), a score of 1.5 was assigned. The scores of individual products in each category (i.e., insecticides or indoor pesticides) were added to obtain a summary frequency index.

Statistical analysis. We performed analyses for overall leukemia and ALL separately. We used conditional logistic regression to estimate ORs and 95% confidence intervals (CI), adjusting for annual household income in U.S. dollars (three categories: < 30,000, 30,000–75,000, > 75,000).

We separated exposure history by specific periods of interest. Patients who were diagnosed during year 1 and their controls were excluded from the analysis of household pesticide exposures during year 1 and the risk of childhood leukemia, because it would be difficult to decide whether the exposures, if any, occurred before diagnosis. Similar exclusions were made for pesticide exposures during the years 2 and 3 as well, producing a smaller study population for subgroup analyses.

Results

Cases and controls were similar regarding age, sex, race, Hispanicity, maternal education, and maternal age (Table 1). Controls have a somewhat higher annual household income.

The percentages of a variety of pesticide exposures during the index child's first year are shown in Table 2. Approximately 40% of the households used pesticides to control ants, flies, or cockroaches, whereas few families administered spider or termite control products. Individual products were grouped into several categories, including insecticides, flea control products, herbicides, indoor pesticides, and outdoor pesticides. More than half of households used insecticides or indoor pesticides during the 1-year period. The percentage of pesticide exposures during other periods varied (detailed data not shown).

Generally, the analyses of overall childhood leukemia and ALL yielded similar results. The use of professional pest control services in each of the five time frames (3 months before pregnancy, pregnancy, and years 1, 2, and 3) was more common in cases than in controls (Table 3). The ORs associated with the use of professional pest control service were > 2 for all periods except for the 3 months before pregnancy. Although the ORs for different periods were not exactly the same, a statistically significant elevated risk of leukemia was observed among children whose houses were professionally treated for pests any time during the 4-year period (OR = 2.8; 95% CI, 1.4–5.7).

The relationship between exposure to insecticides (excluding flea control products) and leukemia risk varied across the five individual time frames, with the highest OR (2.1) observed for exposure during pregnancy and the lowest OR (1.2) for exposure during year 3 (Table 3). Exposure to insecticides (excluding flea control products) any time during the 4-year period was associated with a significantly increased risk of childhood leukemia (OR = 2.1; 95% CI, 1.1–4.3). ORs for each increment in frequency index in all time frames were > 1, which is consistent with the results based on binary categorization of exposures. Compared with ORs for children who were not exposed to insecticides during the 4-year period (i.e., those who were assigned a frequency index of 0), the ORs for children who had a frequency index of 1–5 or > 5 were 1.5 (95% CI, 0.6–3.6) and 2.4 (95% CI, 1.2–5.1), respectively.

The families of controls used more flea control products than did case families, which may be due to the fact that more control families owned cats and/or dogs. The ORs associated with the use of flea control products were smaller than 1, but none were statistically significant.

Table 1. Characteristics of cases and controls.

	Leukemia (162 pairs)			ALL (135 pairs)		
Characteristics	Cases No. (%)	Controls No. (%)	χ^2 test OR[a]	Cases No. (%)	Controls No. (%)	χ^2 test OR[a]
Age[b]			—			—
< 12 months	10 (6)	10 (6)		6 (4)	6 (4)	
12–23.9 months	12 (7)	12 (7)		9 (7)	9 (7)	
2–5 years	86 (53)	86 (53)		80 (59)	80 (59)	
6–10 years	35 (22)	35 (22)		29 (22)	29 (22)	
11–14 years	19 (12)	19 (12)		11 (8)	11 (8)	
Mean (SE) (years)	5.5 (0.3)	5.5 (0.3)		5.3 (0.3)	5.3 (0.3)	
Sex[b]			—			—
Male	93 (57)	93 (57)		79 (59)	79 (59)	
Female	69 (43)	69 (43)		56 (41)	56 (41)	
Race/ethnicity[b]			—			—
Hispanic	48 (30)	49 (30)		40 (30)	40 (30)	
Non-Hispanic white	85 (52)	86 (53)		72 (53)	73 (54)	
Non-Hispanic black	5 (3)	5 (3)		2 (1)	2 (1)	
Other	24 (15)	22 (15)		21 (16)	20 (15)	
Household income ($1,000/year)			$p = 0.04$			$p = 0.08$
< 15	20 (12)	11 (7)	Referent	14 (10)	11 (8)	Referent
15–29.9	31 (19)	20 (12)	0.8 (0.3, 2.1)	28 (21)	15 (11)	1.3 (0.4, 3.8)
30–44.9	25 (15)	16 (10)	0.8 (0.3, 2.5)	18 (13)	13 (10)	0.9 (0.3, 3.0)
45–59.9	21 (13)	25 (15)	0.3 (0.1, 0.8)	19 (14)	17 (13)	0.6 (0.2, 1.8)
60–74.9	22 (14)	25 (15)	0.4 (0.1, 1.0)	19 (14)	22 (16)	0.5 (0.2, 1.5)
≥ 75	43 (27)	65 (40)	0.2 (0.1, 0.6)	37 (28)	57 (42)	0.3 (0.1, 1.0)
Maternal education			$p = 0.59$			$p = 0.84$
≤ High school	59 (36)	52 (32)	Referent	47 (35)	43 (32)	Referent
> High school but < Bachelor's	48 (30)	56 (35)	0.8 (0.4, 1.3)	44 (33)	48 (36)	0.8 (0.5, 1.5)
≥ Bachelor's	55 (34)	54 (33)	0.9 (0.5, 1.6)	44 (33)	44 (33)	0.9 (0.5, 1.7)
Maternal age (years)			$p = 0.52$			$p = 0.56$
< 20	11(7)	11 (7)	Referent	9 (7)	10 (7)	Referent
20–24	33 (21)	23 (14)	1.5 (0.6, 3.9)	27 (20)	20 (15)	1.5 (0.5, 4.4)
25–29	44 (27)	49 (30)	0.8 (0.3, 2.0)	35 (26)	40 (30)	0.9 (0.4, 2.4)
30–34	55 (34)	54 (33)	1.0 (0.4, 2.5)	47 (35)	42 (31)	1.2 (0.4, 3.4)
≥ 35	18 (11)	25 (15)	0.7 (0.2, 2.0)	16 (12)	23 (17)	0.8 (0.3, 2.4)
Unknown	1	0		1	0	
Mean (SE) (years)	28.5 (0.4)	29.5 (0.5)		28.6 (0.5)	29.4 (0.5)	

[a]The ORs are derived from conditional logistic regression models, without adjusting for any other factors. Numbers in the parentheses are 95% CIs. [b]These are the matching variables. Age means age at diagnosis for cases and age at the corresponding dates for controls.

Exposure to herbicides during the 4-year period was not associated with the risk of childhood leukemia, although the ORs for exposure during the 3 months before pregnancy or pregnancy were 1.8 and 1.6, respectively.

Cases were exposed to more indoor pesticides than were the controls in each of the five time frames (Figure 1). The highest OR (OR = 2.2; 95% CI, 1.3–3.6) was seen for indoor pesticide exposures during pregnancy. The association with indoor pesticide exposure during year 2 or 3 was weaker and not statistically significant. When all five time frames were combined, children who were exposed to indoor pesticides had an increased risk of leukemia (OR = 1.8; 95% CI, 1.0–3.4). Compared with ORs for children who were not exposed to indoor pesticides during the 4-year period (i.e., those who were assigned a frequency index of 0), the ORs for children who had a frequency index of 1 to 5 or > 5 were 1.4 (95% CI, 0.6–3.1) and 2.0 (1.0–4.0), respectively. Conversely, the magnitude of association between exposure to outdoor pesticides and the risk of childhood leukemia was small, and all the 95% confidence intervals of the ORs included 1 (Figure 1).

Discussion

Existing studies have generated relatively consistent results, indicating that exposure to household pesticides is associated with an increased risk of childhood leukemia, although the subtype of cases included, definition of exposure, and exposure period of interest differed (*4–7,9–13*). The results from the NCCLS provide additional strong support to the previous observations by distinguishing between the risks associated with different types of pest control, demonstrating a dose–response relationship and indicating the importance of the timing and location of exposure.

In the NCCLS, the use of professional pest control services was significantly associated with an increased risk of childhood leukemia, and the magnitude of association was larger than what was seen for general insecticide or indoor pesticide exposures. It is possible that professional pest control agencies used more concentrated and more persistent compounds, which could also be more carcinogenic. However, it is also likely that the use of professional pest control services reflects the severity of pest problems in a specific household. Professional pest control services generally apply pesticides throughout the entire house, whereas people who apply pesticides themselves are more inclined to target a specific pest infestation. In addition, it may be easier to remember accurately if the family has engaged a professional pest control service than if some family members applied pesticides themselves. Similarly, elevated ORs in the range of 1.26–2.35 were reported for professional treatment against ants and cockroaches in a recently published study of childhood ALL (*12*). In contrast to our findings, the use of household insecticides by professional pest control agencies was not associated with the risk of acute childhood leukemia in a German study that included more than 1,000 cases (*13*). However, the prevalence of the use of professional control services in the German study (2.2% in cases and 1.7% in controls) was markedly lower than what was reported in the NCCLS (33.6% in cases and 21.6% in controls from 3 months before pregnancy through the third birthday), which would result in limited statistical power to detect such an association in Germany.

Exposure to general insecticides during the first few postnatal years is associated with an increased risk of childhood leukemia in the NCCLS, which is consistent with previous studies and showed a dose–response relationship. In addition, the risk for exposure during pregnancy was higher than the risks for exposures after birth. Frequent prenatal use of household pesticides was also linked to an increased risk of ALL in another study (*12*). It may be inferred that the embryo or fetus is especially sensitive or susceptible to carcinogens in the environment. There is evidence that ALL is initiated *in utero* (*14*), and it has been shown that some chromosome translocation events related to the incidence of childhood ALL have a prenatal origin (*15,16*). An ongoing activity of the NCCLS is to determine whether selected translocations can be backtracked to birth. Correlating environmental exposures during pregnancy with chromosome translocations present at birth will likely help illustrate the natural history of childhood leukemia and the timing of key exposures and mutational events.

There is a considerable overlap between the definitions of insecticides and indoor pesticides, and the results regarding indoor pesticide use were similar to what was seen for insecticides. Reported exposure to herbicides during the 4-year period was not associated with leukemia risk, although an elevated and insignificant risk was observed for exposure before and during pregnancy. Consistent with a newly completed ecologic assessment of agricultural pesticide use and childhood leukemia conducted in California (*17*), no significant association between outdoor pesticide exposures and leukemia risk was observed. There could have been some misclassification in terms of indoor and outdoor pesticide use. For example, pesticides used to control rats and mice are usually applied outside of the house, but it is also possible that they are sometimes applied inside. Misclassification between indoor and outdoor exposures would have made the differences between these two categories smaller.

The NCCLS has several design features that are improvements over existing studies. Unlike several previous studies that used random digit dialing to select controls, the NCCLS employed a new protocol to select population-based controls. Controls were randomly selected from the California statewide birth registry, and a methodologic evaluation indicated that the birth certificate controls well represented the population base from which the cases arose (*18*). Only incident cases were included in the NCCLS, and controls were selected concurrently, which significantly

Table 2. Proportion of pesticide exposures during year 1.

Type of exposure	Percent in cases (n = 152[a])	Percent in controls (n = 152[a])	Adjusted OR[b] (95% CI)
Individual exposure			
Professional pest control or extermination	16	11	2.3 (1.1–4.9)
Professional lawn service	9	12	0.9 (0.4–2.0)
Ant, fly, or cockroach control products	38	39	1.1 (0.7–1.9)
Spider control products	1	1	1.5 (0.1–25.6)
Termite control products	1	0	Not calculable
Rat, mouse, gopher, or mole control products	4	7	0.6 (0.2–1.7)
Insect repellent for ticks or mosquitoes	11	8	1.7 (0.6–4.4)
Slug or snail bait	17	16	1.5 (0.8–2.7)
Plant/tree insect or disease control products	7	10	0.8 (0.4–1.6)
Weed control products	18	23	0.7 (0.3–1.7)
Indoor foggers for fleas	5	7	0.6 (0.3–1.8)
Flea collars	11	16	0.6 (0.3–1.2)
Flea soaps or shampoos	11	15	0.8 (0.4–1.5)
Sprays, dusts, or powders for fleas	6	7	1.0 (0.4–2.6)
Combined exposure			
Insecticides	59	50	1.7 (1.0–2.9)
Flea control products	22	28	0.8 (0.5–1.4)
Herbicides	23	33	0.7 (0.4–1.2)
Indoor pesticides	59	51	1.6 (1.0–2.7)
Outdoor pesticides	24	24	1.2 (0.7–2.2)

[a]Ten cases diagnosed under 1 year of age were excluded, as were their matched controls. [b]The ORs were derived from conditional logistic regression models, adjusting for annual household income.

reduced the lag time between diagnosis (corresponding date for controls) and interview. This should have made the reported exposure history more reliable. In contrast to many previous studies that collected data through mailed questionnaire or telephone interview, detailed history on household pesticides exposure was obtained through in-home personal interviews in the NCCLS. In addition, the NCCLS was one of the first studies specifically designed to address critical windows of exposure, that is, the timing of household pesticide exposures relative to a child's conception and development.

Recall bias cannot be ruled out in any case–control study that relies on exposures reported by the subjects, and the NCCLS is no exception. It is possible that the respondents, usually the biologic mothers, falsely claimed or forgot to mention certain exposures depending on whether the child was a patient with leukemia. However, mothers of the controls reported more usage of flea control products than the cases, which is consistent with the increased reported contact with cats and/or dogs in controls. In addition, the ORs associated with exposures to several pesticide categories varied by type and across different time frames, which provided some assurance that the observed associations were not due to general overreporting of exposures among mothers of leukemia cases, but instead may provide evidence for the effects of pesticide exposures at critical periods in a child's development.

A difference in annual household income between cases and controls was observed in this study, hence the decision to adjust for it in the analysis. In addition, a separate analysis was conducted excluding subjects with an annual income of less than $30,000, and the results were not systematically different (data not shown).

Results presented here are limited to broad types of pesticides; no specific chemicals are identified at this stage of analysis. It is certainly preferable to identify specific chemicals associated with the risk of leukemia so that preventive measures could be taken. The names of all products were recorded in the NCCLS, and the Environmental Protection Agency registration number on each of the pesticide containers will be obtained during a follow-up visit to the homes of selected cases and controls, with the ultimate goal of determining the specific chemicals rather than generic types of pesticides associated with increased risks. Based on household inventories conducted in California and Minnesota, the most common home insecticides included piperonyl butoxide, chlorpyrifos, pyrethrins, and propoxur (*19,20*). In California, the insecticides most frequently applied by professional pest control services for structural pest control

Table 3. Exposure to insecticides, flea control products, and herbicides by time and the risk of childhood leukemia.

	Leukemia			ALL		
Type of exposure	Cases	Controls	Adjusted OR[a]	Cases	Controls	Adjusted OR[a]
Professional pest control						
3 months before pregnancy (n = 162/135[b])						
No	146	150	Referent	120	125	Referent
Yes	16	12	1.7 (0.7–3.9)	15	10	1.9 (0.7–4.7)
During pregnancy (n = 162/135[b])						
No	140	148	Referent	115	123	Referent
Yes	22	14	2.2 (1.0–4.8)	20	12	2.3 (0.9–5.4)
Year 1 (n = 152/129[b])						
No	127	136	Referent	107	104	Referent
Yes	25	16	2.3 (1.1–4.9)	22	15	2.1 (1.0–4.7)
Year 2 (n = 140/120[b])						
No	109	125	Referent	91	105	Referent
Yes	31	15	3.6 (1.6–8.3)	29	15	3.3 (1.4–7.7)
Year 3 (n = 116/98[b])						
No	93	101	Referent	77	84	Referent
Yes	23	15	2.2 (1.0–4.7)	21	14	2.1 (1.0–4.7)
3 months before pregnancy to 3 years old (n = 116/98[b])						
No	77	91	Referent	62	74	Referent
Yes	39	25	2.8 (1.4–5.7)	36	24	2.6 (1.2–5.4)
Insecticides (excluding flea control products)						
3 months before pregnancy (n = 162/135[b])						
No	99	113	Referent	82	93	Referent
Yes	63	49	1.8 (1.1–3.1)	53	42	1.7 (1.0–3.1)
Each increment in frequency index			1.2 (1.0–1.5)			1.2 (0.9–1.6)
During pregnancy (n = 162/135[b])						
No	83	106	Referent	67	89	Referent
Yes	79	56	2.1 (1.3–3.5)	68	46	2.3 (1.3–4.0)
Each increment in frequency index			1.1 (1.0–1.2)			1.1 (1.0–1.2)
Year 1 (n = 152/129[b])						
No	62	76	Referent	54	66	Referent
Yes	90	76	1.7 (1.0–2.9)	75	63	1.7 (1.0–2.9)
Each increment in frequency index			1.2 (1.0–1.4)			1.2 (1.0–1.4)
Year 2 (n = 140/120[b])						
No	50	62	Referent	42	53	Referent
Yes	90	78	1.6 (1.0–2.7)	78	67	1.7 (1.0–2.9)
Each increment in frequency index			1.1 (1.0–1.3)			1.1 (1.0–1.3)
Year 3 (n = 116/98[b])						
No	40	44	Referent	33	36	Referent
Yes	76	72	1.2 (0.7–2.1)	65	62	1.1 (0.6–2.1)
Each increment in frequency index			1.0 (0.9–1.2)			1.0 (0.9–1.2)
3 months before pregnancy to 3 years old (n = 116/98[b])						
No	23	36	Referent	18	30	Referent
Yes	93	80	2.1 (1.1–4.3)	80	68	2.2 (1.0–4.6)
Each increment in frequency index			1.0 (1.0–1.1)			1.0 (1.0–1.1)

Continued, next page

purposes are piperonyl butoxide, pyrethrins, chlorpyrifos, and diazinon (*21*).

Parental occupational exposure to chemicals such as pesticides and solvents has also been suggested as a risk factor for childhood leukemia (*2,13,22*). Detailed occupational histories were obtained in the NCCLS, but these data are not yet available for analysis. Children living in agricultural communities can also be exposed to pesticides from agricultural use (*23*). Agricultural pesticide use is high in some areas of California, with over 170,000 children living in communities averaging more than 500 pounds of use per square mile for pesticides classified as probable carcinogens (*24*). It will be more informative when exposures from household, parental occupations and nearby agricultural applications can be evaluated jointly, which is a goal of the NCCLS. Ultimately, studies with environmental or biologic monitoring are needed to determine the relationship between pesticide exposure and childhood leukemia.

Another potential limitation of the study is the relatively small sample size, which reduces the power of the study to detect low-level risks. On the other hand, this study did consistently detect risks of 2-fold or greater, and the matched design improves the precision of statistical analyses (*25*). The NCCLS is currently underway and will enroll subjects until 2003. The expansion of the study population, added detail on chemical constituents, and more specific and complete exposure classification will provide more information

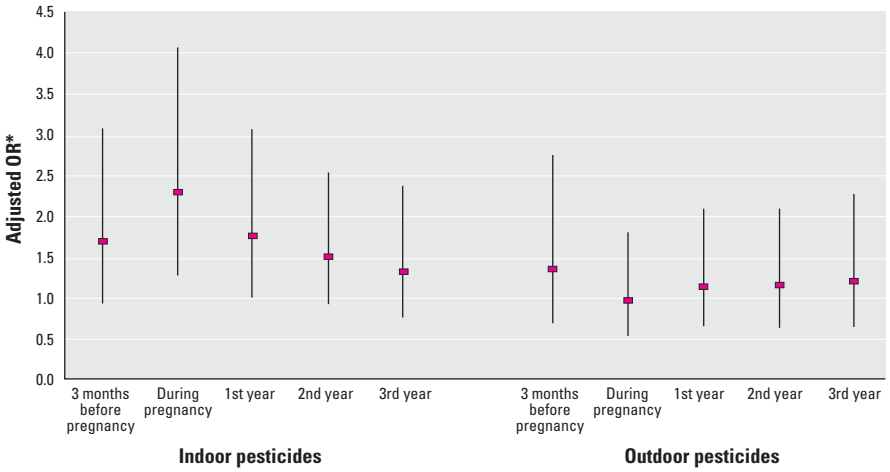

Figure 1. Indoor and outdoor pesticide exposures and the risk of childhood ALL. The boxes are estimated ORs; vertical bars reflect upper and lower limits of 95% CIs.
*Adjusted for annual household income.

Table 3. *Continued.*

Type of exposure	Leukemia Cases	Leukemia Controls	Leukemia Adjusted OR[a]	ALL Cases	ALL Controls	ALL Adjusted OR[a]
Flea control products						
3 months before pregnancy (n = 162/135[b])						
No	136	130	Referent	113	106	Referent
Yes	26	32	0.9 (0.5–1.7)	22	29	0.8 (0.4–1.6)
During pregnancy (n = 162/135[b])						
No	135	128	Referent	113	105	Referent
Yes	27	34	0.8 (0.4–1.4)	22	30	0.7 (0.4–1.4)
Year 1 (n = 152/129[b])						
No	118	110	Referent	98	91	Referent
Yes	34	42	0.8 (0.5–1.4)	31	38	0.9 (0.5–1.6)
Year 2 (n = 140/120[b])						
No	105	98	Referent	88	83	Referent
Yes	35	42	0.9 (0.5–1.5)	32	37	1.0 (1.5–1.8)
Year 3 (n = 116/98[b])						
No	90	81	Referent	74	68	Referent
Yes	26	35	0.8 (0.4–1.4)	24	30	0.9 (0.5–1.7)
3 months before pregnancy to 3 years old (n = 116/98[b])						
No	76	71	Referent	62	59	Referent
Yes	40	45	0.9 (0.5–1.6)	36	39	1.0 (0.5–1.8)
Herbicides						
3 months before pregnancy (n = 162/135[b])						
No	131	139	Referent	111	117	Referent
Yes	31	23	1.8 (0.9–3.5)	24	18	1.6 (0.8–3.3)
During pregnancy (n = 162/135[b])						
No	128	133	Referent	105	112	Referent
Yes	34	29	1.6 (0.9–3.0)	30	23	1.8 (0.9–3.5)
Year 1 (n = 152/129[b])						
No	117	102	Referent	97	86	Referent
Yes	35	50	0.7 (0.4–1.2)	32	43	0.8 (0.4–1.4)
Year 2 (n = 140/120[b])						
No	100	95	Referent	84	80	Referent
Yes	40	45	1.1 (0.7–2.0)	36	40	1.1 (0.6–2.0)
Year 3 (n = 116/98[b])						
No	83	81	Referent	67	67	Referent
Yes	33	35	1.1 (0.6–2.1)	31	31	1.2 (0.6–2.3)
3 months before pregnancy to 3 years old (n = 116/98[b])						
No	78	75	Referent	63	61	Referent
Yes	38	41	1.0 (0.6–1.8)	35	37	1.0 (0.6–1.8)

[a]The ORs were derived from conditional logistic regression models, adjusting for annual household income; numbers in parentheses are 95% CIs. [b]Number of case–control pairs available for the specific analysis.

regarding pesticide exposures and the risk of childhood leukemia.

In summary, the findings from the present study suggest that exposure to household pesticides is associated with an elevated risk of childhood leukemia and further indicate the importance of the timing and location of exposure.

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